Global Access & Partnerships

Program Overview: HIV Medicine Access

MAY 2013

janssen
PHARMACEUTICAL COMPANIES
OF Johnson&Johnson

AT JANSSEN, WE ARE COMMITTED

to helping people living with HIV/AIDS through effective and sustainable access to our HIV medicines.

We believe this requires two important components: ensuring quality and affordable medicines are available sustainably, and that these medicines are used in the most appropriate way in people living with HIV/AIDS (PLWHA). In 2006, we launched a global HIV drug access program, the Global Access and Partnerships Program (GAPP or The Program), to fulfill our responsibility to PLWHA in resource-limited settings. GAPP's HIV drug access efforts are focused on countries with the highest rates of HIV infection and economic vulnerability, such as sub-Saharan Africa (SSA), least developed countries (LDCs), and lower middle-income countries (LMICs). A variety of factors influence our approach to HIV drug access — including the approved indications of each of our medicines and how they are used in clinical practice.

Current Status of HIV Epidemic in Resource-Limited Countries

- More than 8 million people living with HIV in low- and middle-income countries were receiving treatment at the end of 2011. Another 7 million are in need of treatment.
- In 2011, for the first time, a majority (54%) of people eligible for antiretroviral therapy in low- and middle-income countries were receiving it.
- Outside of the Americas, 97% of PLWHA receiving treatment are on first-line therapy; 3% are receiving second-line.
- UNAIDS estimates that the need for second-line is growing in resource-limited settings, such as SSA.

Source: World Health Organization & UNAIDS.

In 2012, Johnson & Johnson was ranked second among 20 global companies in the biannual Access to Medicine Index based on significant progress and improvements made to our access to medicines strategies, R&D portfolio, and philanthropy initiatives.

Janssen's HIV Drugs in Resource-Limited Countries

More PLWHA have access to HIV medicines than ever before. Access to HIV medicines for PLWHA who are new to treatment ("first-line") remains the top public health priority for countries with high HIV burdens. Yet, over time many patients will need to switch to a new "second-line" regimen.

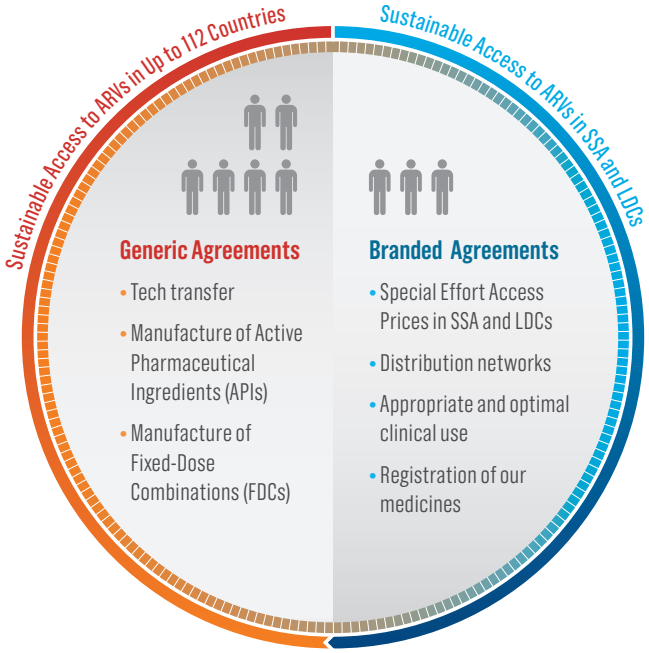
The Program has a portfolio of three HIV treatments. Currently, the protease inhibitor PREZISTA® *(darunavir)* and non-nucleoside reverse transcriptase inhibitor (NNRTI) INTELENCE® *(etravirine)* are indicated in resource-limited countries for use in treatment-experienced adult patients only after previous drug combinations have failed. They are often the last treatment option for patients in these countries. The Company's third HIV medicine, the NNRTI EDURANT™ *(rilpivirine)*, received its first regulatory approvals in the United States and Europe for treatment-naïve adult patients in 2011.[1] EDURANT™ has received its first regulatory approvals in Latin America and other regulatory filings have begun across the world, including Asia, Latin America and the Caribbean, and sub-Saharan Africa.

One of our key responsibilities is to facilitate access to these medicines once they are approved in a way that safeguards their clinical effectiveness today and for the future.

[1] As actual approved uses are determined by local regulatory authorities, please see package insert for precise indication.

Guiding Principle: Treatment Standardization
(Simplification & Optimization)

We believe that standardization through simplifying and optimizing HIV therapy is in the best interest of people living with HIV and public health systems. We support the WHO's (Treatment 2.0) goal of effective, affordable, single pill, once-daily HIV regimens for resource-limited countries. In support, we are collaborating on new fixed-dose combinations (FDCs) with our HIV medicines. We also support global initiatives working to potentially standardize regimens for first-, second-, and third-line therapy.



Key Elements of Janssen's HIV Drug Access Program

1. Licensing for Branded and Generic HIV Medicines
2. Priority Registration
3. Reduced Special Effort Access Pricing
4. Medical Education and Clinical Research

Key Program Elements

GAPP aims to improve the health of people worldwide through sustainable availability of our HIV medicines, medical education on appropriate and safe use of these medicines, and innovative collaborations.

Licensing for Branded and Generic HIV Medicines

Licensing is a key pillar of our Program's strategy. Agreements for **our branded HIV medicines** at Special Effort Access Prices in SSA and LDCs have provided rapid access for patients in need during the Program's formative years. These royalty-free agreements have helped to establish distribution networks, lay the groundwork for the appropriate clinical use of our HIV medicines, and support appropriate, associated pharmacovigilance activities. They have also accelerated the registration process of our branded HIV medicines. Registering our branded medicines is an important first step in facilitating the introduction of quality generic versions of our medicines. These agreements were designed to ensure timely and sustainable access to all our HIV medicines in SSA, which is the region with the highest HIV burden and economic vulnerability, and LDCs.

For *rilpivirine,* our HIV medicine indicated for treatment-naïve adults as part of combination HIV treatment and with greater anticipated volumes, we have additional licenses for the manufacture of **generic versions.** These agreements, covering as many as 112 countries, offer licensees the technical information and knowledge ("tech transfer") to manufacture the active pharmaceutical ingredients (API) and finished product. They also enable development of appropriate fixed-dose combinations (FDCs) of our products with other HIV medicines within the licensed territories. Licensing to globally-recognized generic manufacturers supports a sustainable supply of affordable and quality generic versions of our HIV medicines.

All of our agreements go beyond simply licensing our patents; they strive to ensure that critical components of HIV drug access are achieved, including timely in-country registration, supply chain development, and drug safety monitoring. We believe our agreements and efforts provide the best route to expanding access to our medicines in resource-limited countries.

For *darunavir,* our HIV medicine for treatment-experienced adults, Janssen announced in 2012 that it would not enforce our patents and control on the drug provided the *darunavir* product is medically acceptable and is used only in SSA and LDCs. This policy assures generic manufacturers that they may manufacture high quality *darunavir* that is used in SSA and the LDCs without a concern that we will accuse them of infringing on *darunavir* patents.

Priority Registration

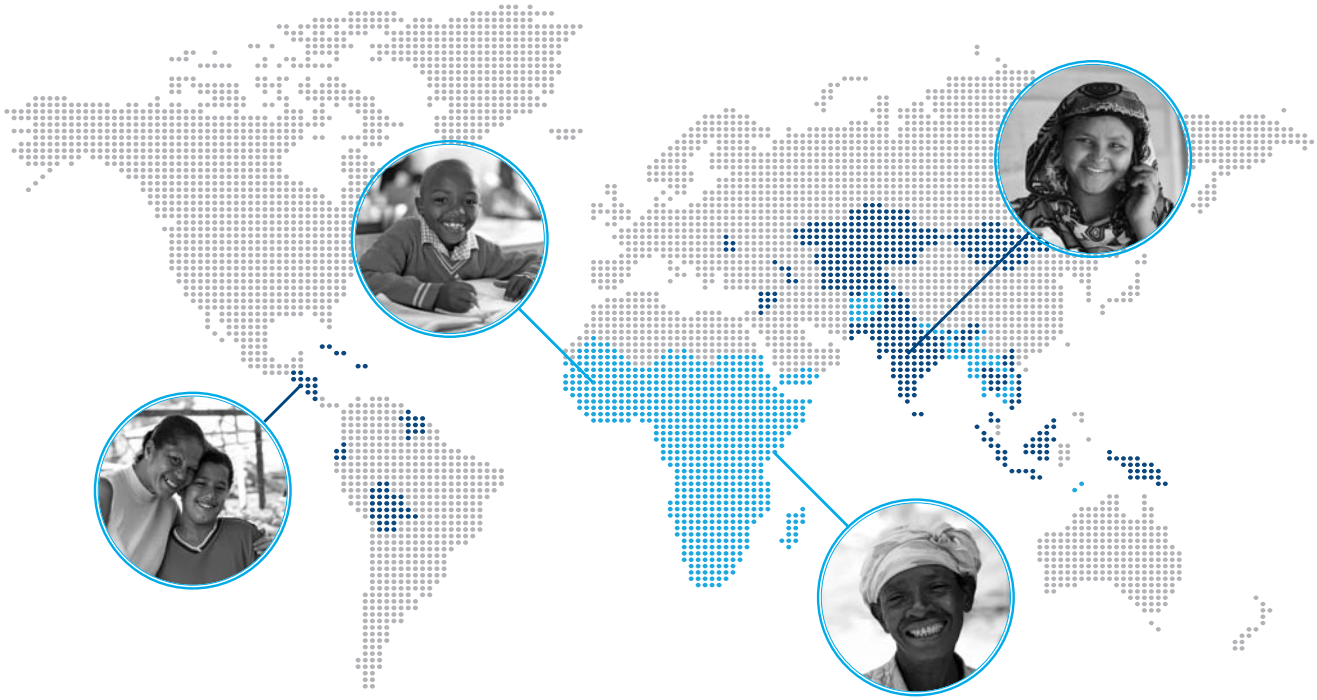
A comprehensive, multi-country registration effort facilitates availability of our branded HIV medicines where there is a public health need. Our Program has prioritized registration efforts in those countries with the greatest HIV burden, economic vulnerability, and immediate need for third-line drugs, such as PREZISTA® *(darunavir)* and INTELENCE® *(etravirine)*. In SSA, we target 23 countries

On November 29, 2012, the Janssen Pharmaceutical Companies of Johnson & Johnson announced their intention not to enforce the patents they own on the antiretroviral (ARV) drug *darunavir* provided the *darunavir* product is medically acceptable and is used only in SSA and LDCs. This announcement is intended to assure generic manufacturers that they may manufacture high quality *darunavir* product used in SSA and LDCs without a concern that they will be accused of infringing on *darunavir* patents.

Summary of Key Elements of Branded & Generic Licenses and Enabled Generics (as of May 2013)

	Special Access Branded Products			Generic Versions of Our HIV Products		
	PREZISTA® *(darunavir)*	INTELENCE® *(etravirine)*	EDURANT™ *(rilpivirine)*	*Darunavir* License	*Darunavir* IP Waiver	*Rilpivirine* License
Number of Licenses/ Enabled Generics	1[3]	1[4]	1[5]	1[6]	Unlimited[7]	5[8]
Original Agreement Date	2007	2009	2011	2008	2012	2011
Country Scope	SSA & LDCs	SSA & LDCs	SSA & LDCs	India	SSA & LDCs	112
PLWHA in LMIC Covered[2]	76%	76%	76%	8%	76%	88%
Non-Exclusive	■	■	■	■	■	■
Janssen Single Agent Formulations Approved by FDA and/or EMA	■	■	■	■	■	■
Royalty-Free	■	■	■		■	
Enables FDC Development				■	■	■
Enables Tech Transfer				■	■	■
Enables API Manufacture				■	■	■

[2] Calculated using PLWHA data from *UNAIDS Report on the Global AIDS Epidemic 2010,* Annex 1: HIV and AIDS Estimates and Data, 2009. Low- and middle-income countries (LMIC) determined using World Bank classification, including low-income, lower-middle income and upper-middle income countries | [3] Aspen Pharmacare Ltd. | [4] Ibid. | [5] Ibid. | [6] Emcure Pharmaceuticals Ltd. | [7] Waiver applies to any generic manufacturer, provided generic versions of *darunavir* produced or supplied are quality, medically acceptable, and used only in the defined territory | [8] Aspen Pharmacare Ltd., Emcure Pharmaceuticals, Ltd., Mylan Laboratories Ltd. (formerly Matrix), Hetero Drugs Ltd., and Strides Arcolab Ltd.



● Branded and Generic Territory ● Expanded Generics Territory

Fixed-Dose Combinations (FDCs)

● As part of our efforts to simplify HIV treatment options for patients, we are engaging in multiple clinical collaborations with Gilead Sciences, Inc. to develop new FDC products. FDCs are important as they support adherence and are preferred by public health treatment programs. Our first agreement was for the development of, and access to, COMPLERA® *(emtricitabine/rilpivirine/tenofovir disoproxil fumarate)*, which has received approval in the U.S and Europe for treatment-naïve patients.[9] We are also working on the development of a new FDC of *darunavir* and Gilead's *cobicistat*, an investigational "boosting" agent. Janssen has a license agreement with Gilead for the development of a single tablet FDC regimen containing *darunavir*, Gilead's *emtricitabine*, the investigational drug *tenofovir alafenamide*, and *cobicistat*.

for priority registration. For those countries with limited public health need, and where local regulations allow, our products may be available through pre-approval access mechanisms. The 400mg tablet of PREZISTA® for use in treatment-experienced adult patients was approved by the U.S. Food and Drug Administration (FDA) in 2010 and the European Medicines Agency (EMA) in 2011. Registration filings for this 400mg dose have begun in SSA.

EDURANT™ *(rilpivirine)* received its first regulatory approvals in the United States and Europe in 2011. This is an important first step, as many resource-limited countries require EMA and/or FDA approval documentation to submit local regulatory dossiers. Regulatory filings for EDURANT™ are ongoing worldwide.

In 2012, we reached a significant milestone in our efforts to provide affordable and sustainable access to quality HIV medicines as four tablet strengths of our HIV medicines PREZISTA® *(darunavir)* and INTELENCE® *(etravirine)* were included in the World Health Organization (WHO) List of Prequalified Medicinal Products. Having our HIV medicines on this list facilitates both the registration and procurement process as several countries require HIV medicines to be WHO prequalified.

Reduced Special Effort Access Pricing

The Program operates on a sustainable basis and does not generate a profit. In SSA and LDCs, we offer our branded HIV medicines at Special Effort Access Prices, which are significantly reduced from those in the U.S. and Europe. We are committed to lowering our Special Effort Access Prices, as volume or cost-savings in manufacturing allow.

- In October 2011, we **reduced the Special Effort Access Price** of PREZISTA® *(darunavir)* by 26% — to US$2.22 (ex-factory) for the 1200mg daily dose.

[9] In the European Union, the *emtricitabine/rilpivirine/tenofovir disoproxil fumarate* FDC is registered under the brand name Eviplera®.

Summary of Branded Product Registration Status (as of May 2013)

	PREZISTA® *(darunavir)*			INTELENCE® *(etravirine)*	EDURANT™ *(rilpivirine)*
Tablet Strength	Adult (300mg and/or 600mg)	Adult (400mg)	Pediatric (75mg and 150mg)	Adult (100mg)	Adult (25mg)
FDA Approval	Jun. 2006	Oct. 2008	Dec. 2008	Jan. 2008	May 2011
EMA Approval	Feb. 2007	Jan. 2009	Jun. 2009	Aug. 2008	Nov. 2011
Initial GAPP Filing	2007	2012	2011	2009	2011
SSA & LDCs					
Approvals	21	0	0	16	0
Approvals Pending	2	3	3	6	3
LMICs[10]					
Approvals	16	10	5	12	4
Approvals Pending	0	3	6	3	8

- In July 2012, we **reduced the Special Effort Access Price** of INTELENCE® *(etravirine)* by 52% — to US$1.20 (ex-factory) for the 400mg daily dose.

Beyond SSA and LDCs, we provide reduced prices for our branded HIV medicines through differential pricing that considers local economic development, HIV treatment programs, and public health need. Prices in individual countries are subject to local pricing and reimbursement discussions.

Medical Education & Clinical Research

Our HIV medicines require physicians to understand how to manage patients who have failed previous HIV treatment regimens. To assist with this, we jointly support Continuing Medical Education on appropriate and safe use of HIV medicines with Aspen Pharmacare and others. Specifically, we collaborate with the St. Stephens AIDS Trust (U.K.) on accredited workshops on HIV drug resistance and use of HIV third-line treatment in SSA. These workshops have trained approximately 500 physicians in 21 SSA countries. Additional workshops are planned for 2013.

We also support, or conduct, clinical research on the appropriate and safe use of our approved HIV medicines in resource-limited countries.

We share clinical data to support inclusion in global, regional, and national HIV treatment guidelines, which are essential in designing effective HIV treatment strategies. In 2010, PREZISTA® and INTELENCE® were mentioned in WHO Guidelines for HIV Treatment[11] as potential candidates for use in highly treatment-experienced adult and pediatric patients ("third-line"). They are not included in the guidelines for first- or second-line treatment.

Pediatric HIV Treatment

Our pediatric tablet formulations of PREZISTA® (75mg and 150mg tablets) are approved for treatment-experienced patients six to 18 years old, and regulatory submissions in resource-limited countries are underway. In December 2011, a twice daily regimen of PREZISTA® 100mg/ml oral suspension for use in treatment-experienced patients three to six years of age was approved by the FDA. In 2012, PREZISTA® 75 mg and 150 mg tablets, in combination with low-dose *ritonavir* and other antiretrovirals, were included in the WHO List of Prequalified Medicinal Products for treatment-experienced pediatric patients. In March 2012, INTELENCE® 25mg scored and dispersible tablet for treatment-experienced children and adolescents aged six to 18 years of age also received FDA approval. We are currently investigating a potential pediatric formulation of our HIV medicine EDURANT™ *(rilpivirine)*.

[10] Please see "Current Generic Licensing Territories for *Rilpivirine* (112 Countries)" table for Program territories beyond SSA and LDCs.

[11] Antiretroviral Therapy for HIV Infection in Adults and Adolescents: Recommendations for a public health approach: 2010 revision. World Health Organization.

HIV Resistance and Diagnostics

Antiretrovirals, or HIV medicines, are designed to stop the HIV virus from replicating. The HIV virus replicates frequently, which can lead to mistakes, or mutations, in the virus sequence. Some of these mutations can enable the virus to become resistant to one or more HIV medicines. This means the medicine no longer works and the virus starts replicating again, which is called "HIV drug resistance." Understanding how HIV medicines work — and why they fail — is essential to providing effective and optimal HIV treatment. Janssen Diagnostics has long supported and provided technical assistance on resistance diagnostics, surveillance, and monitoring to better understand HIV resistance and resistance patterns in resource-limited settings. As a result, Janssen Diagnostics has built a database with the world's largest collection — approximately 500,000 — of HIV virus sequences of which approximately 5% are non-B subtype, the most prevalent genotype in resource-limited countries. Janssen Diagnostics shares the information in this database through collaborations with research groups worldwide.

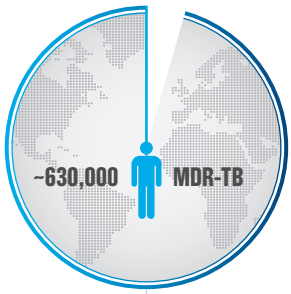
Tuberculosis and Opportunistic Infections

Janssen also has established R&D collaborations and activities to develop new and improved treatments for infectious diseases that disproportionately affect patients with HIV in resource-limited countries.

New Research & Collaborations for Tuberculosis (TB)

In December 2012, the FDA granted accelerated approval to SIRTURO™ *(bedaquiline; TMC207)* for the treatment of pulmonary multi-drug resistant tuberculosis

(MDR-TB) as part of combination therapy in adults. SIRTURO™ has the potential to address some of the unmet needs in the field of TB. Today, treatment of MDR-TB



Globally, there are ~630,000 cases of MDR-TB, but only ~56,000 received treatment in 2011.

Source: World Health Organization. (2012)

requires up to six second-line drugs for up to two years, which poses a severe burden for patients and health systems.

We have a collaboration with the Global Alliance for TB Drug Development (TB Alliance) to share expertise and resources in the development of TMC207 for drug-susceptible TB. In addition, Janssen will collaborate with the TB Alliance on a discovery research program to identify new compounds for the treatment of TB. The rights for the newly discovered compounds for the treatment of tuberculosis will belong to the TB Alliance under a royalty-free license. Costs for the development of *bedaquiline* will be shared.

MicMAT (Tibozole™)

Oral candidiasis or "thrush" is the most common and debilitating opportunistic infection in HIV patients not receiving HIV medicines in the developing world. MicMAT (*miconazole nitrate* 10mg, muco-adhesive-buccal tablet), indicated for the treatment of oral candidiasis, is designed specifically to meet the unique needs of PLWHA in the developing world. More than

3.5 million MicMAT treatments have been made available through not-for-profit prices and donation programs.

HIV Prevention

Partnerships for HIV Prevention

We are working to prevent the spread of HIV, and reduce the burden of HIV on women and their families. Microbicides are an innovative HIV prevention tool being investigated in various forms such as sustained-release vaginal rings to help prevent sexual transmission of HIV. The Company led the way in antiretroviral microbicides research. In 2004, it formed one of the very first public-private collaborations in the microbicides field with the International Partnership for Microbicides (IPM). The program provided IPM with a royalty-free license for TMC120 *(dapivirine)* to develop, manufacture, and distribute the compound as a vaginal microbicide in developing countries. The monthly *dapivirine* ring is now being evaluated in two parallel efficacy trials in multiple countries in Africa, with results expected in 2015.

***Rilpivirine* (RPV, TMC278) Long-Acting**

Janssen recognizes that a long-acting, low-dose HIV medicine may someday play a role in pre-exposure prophylaxis (PrEP). Exploratory studies of an investigational long-acting, injectable formulation of *rilpivirine* (RPV-LA) are currently underway. A study[12] presented at the 19th Conference on Retroviruses and Opportunistic Infections (CROI) in 2012, shared data supporting ongoing exploration of RPV-LA as a potential PrEP agent. The RPV-LA project is currently in the early stages of development and additional studies are needed to determine the next steps in the development of RPV-LA as a potential PrEP candidate.

Current Generic Licensing Territories for *Rilpivirine* (112 Countries)

Africa
Angola
Benin
Botswana
Burkina Faso
Burundi
Cameroon
Cape Verde
Central African Republic
Chad
Comoros
Congo
Congo, DRC
Cote d'Ivoire
Djibouti
Equatorial Guinea
Eritrea
Ethiopia
Gabon
Gambia
Ghana
Guinea
Guinea-Bissau
Kenya
Lesotho
Liberia
Madagascar
Malawi
Mali
Mauritania
Mauritius
Mozambique
Namibia
Niger
Nigeria
Rwanda
Sao Tome and Principe
Senegal
Seychelles
Sierra Leone
Somalia
South Africa
South Sudan
Sudan
Swaziland
Tanzania
Togo
Uganda
Zambia
Zimbabwe

Asia Pacific
Bangladesh
Cambodia
Fiji
India
Indonesia
Kiribati
Laos
Myanmar
Nauru
Nepal
Palau
Papua New Guinea
Sri Lanka
Samoa
Solomon Islands
Thailand
Timor-Leste
Tonga
Tuvalu
Vanuatu
Vietnam

Eastern Europe, Central Asia Middle East
Afghanistan
Armenia
Bhutan
Georgia
Kazakhstan
Kyrgyz Republic
Maldives
Moldova
Mongolia
Pakistan
Syria
Tajikistan
Turkmenistan
Uzbekistan
Yemen

Latin America & Caribbean
Anguilla
Antigua and Barbuda
Aruba
Bahamas
Barbados
Belize
Bolivia
British Virgin Islands
Cuba
Dominica
Dominican Republic
Ecuador
El Salvador
Grenada
Guatemala
Guyana
Haiti
Honduras
Jamaica
Montserrat
Nicaragua
St. Kitts and Nevis
St. Lucia
St. Vincent and the Grenadines
Suriname
Trinidad and Tobago
Turks and Caicos

[12] Jackson A, Else L, Tjia J, Seymour N, Stafford M, Back D, Gazzard B, Boffito M. *Rilpivirine-LA* formulation: Pharmacokinetics in plasma, genital tract in HIV_ females and rectum in males [abstract]. In: 19th Conference on Retroviruses and Opportunistic Infections; 2012 Mar 5-8; Seattle, WA. Abstract nr 35.

Antiretroviral (ARV) Indications for SSA*

● PREZISTA® *(darunavir)*

PREZISTA®, co-administered with 100mg *ritonavir* (PREZISTA®/rtv), and with other antiretroviral agents, is indicated for the treatment of human immunodeficiency virus (HIV) infection in antiretroviral treatment-experienced adult patients, such as those with HIV-1 strains resistant to more than one protease inhibitor. This indication is based on week 24 analyses from 2 controlled clinical trials in treatment-experienced, HIV-1 infected patients, where PREZISTA®/rtv showed a significantly greater reduction of plasma HIV RNA levels and greater increase in CD4+ cell counts when compared to a protease inhibitor (PI) regimen of choice, each given in combination with other antiretroviral drugs. Additional data is available from open label studies. Clinical studies on the use of PREZISTA®/rtv in HIV infected pediatric patients and in antiretroviral treatment naïve adult patients are ongoing.

● INTELENCE® *(etravirine)*

INTELENCE®, in combination with a boosted protease inhibitor and other antiretroviral medicinal products, is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-experienced adult patients, including those with non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance. This indication is based on week 48 analyses from 2 randomized, double-blind, placebo-controlled Phase III trials in treatment-experienced patients with NNRTI resistance (present at screening and/or archived) and protease inhibitor (PI) resistance, where INTELENCE® administered with a background regimen (BR) was statistically superior to placebo with a BR in terms of the proportion of patients achieving a confirmed undetectable viral load (< 50 HIV-1 RNA copies/ml) and the increase in CD4 cell counts from baseline. Treatment history and, when available, resistance testing, should guide the use of INTELENCE®. The use of other active antiretroviral agents with INTELENCE® is associated with an increased likelihood of treatment response. The risks and benefits of INTELENCE® have not been established in pediatric patients or in treatment naïve adult patients.

● EDURANT™ *(rilpivirine)*

EDURANT™, in combination with other antiretroviral medicinal products, is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-naïve adult patients with a viral load ≤ 100,000 HIV-1 RNA copies/ml. As with other antiretroviral medicinal products, genotypic resistance testing should guide the use of EDURANT™. EDURANT™ is currently approved in over 48 countries worldwide, including Bolivia, the European Union, Honduras, Nicaragua, and the U.S.

● SIRTURO™ *(bedaquiline)*

SIRTURO™ is indicated in adults (≥ 18 years) as part of combination therapy of pulmonary tuberculosis due to multi-drug resistant *Mycobacterium tuberculosis*.

* Please note that registration conditions of PREZISTA®, INTELENCE®, and EDURANT™ differ internationally. Not all indications and dosage forms presented for these products are currently approved in Malaysia. Please refer to Malaysia Package Insert(s) for more details.

Art accreditation: *Peyi, Blue Rhapsody*
Janssen is proud to feature artwork created by people affected by the illnesses and diseases we are committed to treating and preventing.

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700 Route 202
Raritan, NJ, 08869
United States
www.janssen.com